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Which Stress Test is Superior for Perioperative Cardiac Risk Stratification in Patients Undergoing Major Vascular Surgery?

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Objective: *to compare the additional prognostic value of Dobutamine Stress Echocardiography (DSE), Dipyridamole Stress Echocardiography (DiSE) and Perfusion Scintigraphy (DTS) on clinical risk factors in patients undergoing major vascular surgery.*
Design: *retrospective analysis.*
Materials: *2204 consecutive patients who underwent DSE (n = 1093), DiSE (n = 394), or DTS (n = 717) testing before major vascular surgery were studied.*
Methods: *primary endpoint was a composite of cardiac death and non-fatal myocardial infarction (MI). Logistic regression analysis was performed to evaluate the relation between cardiac risk factors, stress test results and the incidence of the composite endpoint.*
Results: *there were 138 patients (6.3%) with cardiac death or MI. Patients with 0, 1–2, and 3 or more risk factors experienced respectively 3.0, 5.7 and 17.4% cardiac events. We found no statistically significant difference in the predictive value of a positive test result for DiSE and DSE (Odds ratio (OR) of 37.1 [95% CI, 8.1–170.1] vs 9.6 [95% CI, 4.9–18.4]; p = 0.12), whereas a positive test result for DTS had significantly lower prognostic value (OR = 1.95 [95% CI, 1.2–3.2]).*
Conclusion: *a result of stress echocardiography effectively stratified patients into low- and high-risk groups for cardiac complications, irrespective of clinical risk profile. In contrast, the prognostic value of DTS results was more likely to be dependent on patients' clinical risk profile.*

Key Words: Prognosis; Major vascular surgery; Risk assessment; Dobutamine stress echocardiography; Dipyridamole stress echocardiography; Dipyridamole perfusion scintigraphy.

Introduction

Patients undergoing major vascular surgery are at increased risk of cardiovascular complications, such as cardiac death and nonfatal myocardial infarction (MI), due to underlying coronary artery disease (CAD).[1] These complications may occur during or directly after surgery. Evaluation of CAD is often difficult since patients have limited exercise capacity. Therefore, multiple non-exercise dependent stress tests have been developed. It has been suggested that the most accurate information on the individual patient's risk can be obtained by a combination of clinical characteristics and results of dipyridamole perfusion scintigraphy (DTS).[2] Recently, the use of pharmacological stress echocardiography either with dipyridamole (DiSE)[3–6] or dobutamine (DSE)[7–13] has been proposed for risk stratification.

Pharmacological stress echocardiography has proved to be a safe and sensitive technique for predicting perioperative cardiac events, with an excellent negative predictive power.[6,9] However, it has not been well established, which of the available tests is best for predicting perioperative cardiac complications. The purpose of this investigation was to compare the ability of dipyridamole and dobutamine stress echocardiography, and dipyridamole stress perfusion scintigraphy to predict perioperative cardiac events in large cohorts of patients undergoing major vascular surgery.

Materials and Methods

Description of the study population

The study population consisted of 2204 consecutive patients undergoing preoperative screening with one

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of the noninvasive tests before their scheduled abdominal aortic surgery or infrainguinal procedure.

Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed according to study protocol in 1093 consecutive patients who participated in the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography study (DECREASE) between 1996 and 1999.[9,14] Two investigators who were aware of the doses of dobutamine and atropine used during tests were blinded to clinical information and performed off-line assessment of echocardiographic images. The left ventricle was divided into 16 segments and wall motion was scored on a 5-point ordinal scale; (1) normal wall motion; (2) mild hypokinesis; (3) severe hypokinesis; (4) akinesis and (5) dyskinesis. For each patient, a wall motion score index was calculated at rest and during peak stress. The results of DSE were considered positive if new wall-motion abnormalities (NWMAs) occurred.

Dipyridamole stress testing

Dipyridamole stress echocardiography
Dipyridamole stress echocardiography was performed according to study protocol in 394 prospectively enrolled patients who participated in the Echo Persantin International Cooperative study (EPIC) between 1994–1998.[6] Patients were screened with DiSE prior to their scheduled vascular surgery.[15] During the procedure, 2-dimensional echocardiographic, 12-lead ECG, and blood pressure monitoring were continuously performed. Regional wall motion and test positivity was assessed for DiSE testing. Aminophylline was given at the end of the test. Assessment of stress echocardiography performance was performed using predefined criteria for stress echocardiography reading.[16]

Dipyridamole thallium perfusion scintigraphy
Dipyridamole thallium-201 scintigraphy was performed in 717 consecutive patients between 1984 and 1991, who were referred to DTS testing before major elective vascular surgery at the following institutes: University of Massachusetts Medical Center ($n = 360$),[17] Massachusetts General Hospital ($n = 246$),[2] Medical Center Hospital of Vermont ($n = 111$).[18] Baseline clinical and test characteristics were prospectively collected for all but one study.[2] The DTS test was performed according to a previously described standardised protocol.[19,20] The test was administered and interpreted by experienced nuclear cardiologists who were blinded to the patients' clinical course. Planar thallium imaging was used at all centres. Initial images were obtained in three standard views (anterior, left anterior oblique, and lateral) immediately after the administration of dipyridamole and thallium, and delayed images were obtained on average 3 h later. A positive test result for DTS was defined as planar myocardial scintigraphic images, revealing images exhibiting defects, which were partially or completely redistributed on delayed (> 3 h) images.

Definition of cardiac endpoint

For the present study, a composite of cardiac death and nonfatal myocardial infarction (MI) occurring within 30 days after surgery was chosen. Cardiac death was defined as death directly attributable to myocardial infarction, congestive heart failure, or ventricular arrhythmia in the absence of any other precipitating factor. Myocardial infarction was diagnosed by either serum creatinine-kinase level of more than 110 U/L with a myoglobin isoenzyme fraction of more than 10%, or by new electrocardiographic Q waves ≥ 1 mm, or faster than 30 ms in duration.

Clinical risk factors

Potential clinical determinants of perioperative cardiac events were selected by review of the current published literature, and included: advanced age (> 70 years), a current or stable angina pectoris (AP), a history of MI, a history of heart failure, and a history of diabetes mellitus (DM). Current stable angina pectoris was characterised according to the Canadian Cardiovascular Society Angina Classification.[21] History of MI was defined as a documented history of a MI or a finding of pathologic Q waves on electrocardiography. Congestive heart failure was defined according to the presence of a history of symptoms or signs of pulmonary congestion, signs of left or right ventricular failure and chest radiographic findings suggestive of heart failure. Diabetes mellitus was defined by a predefined criterion used in each study.

Statistical analysis

Differences in baseline clinical characteristics between the study populations were evaluated by

Kruskal–Wallis tests or Chi-square tests as appropriate. Despite the observed differences, we considered the patients in the separate datasets to be representative of all patients undergoing elective vascular surgery. Thus, the individual datasets were combined. Univariate and multivariate logistic regression analyses were performed to study the prognostic value of the selected clinical characteristics with respect to composite endpoint. Information on heart failure was missing in 35% of patients. In order to include heart failure in the regression analysis missing values were imputed based on the mean value (0.072) of patients either with (value 1) or without (value 0) a history of heart failure. All clinical variables entered the multivariate model irrespective of the results of the univariate analyses. Based on the results of the multivariate analysis a simple clinical risk score was composed. Subsequently, logistic regression analyses were applied to predict the prognostic value of a positive test result. Differences in prognostic value between the tests (DSE, DiSE, DTS) were evaluated by comparing the regression coefficients associated with the test result using the *t*-test. Finally, the additional prognostic value of a positive test result upon the clinical risk score was studied by additional logistic regression analyses. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are reported. The predictive power of regression models was quantified by the c-index, which is identical to the area under the receiver operating characteristic curve; the c-index ranges from 0.5 (not predictive at all) to 1.0 (optimal performance).

Results

There were important differences in clinical baseline characteristics and test results between the populations (Table 1). Patients in the DSE group were older, and more often had a history of MI than patients undergoing either DiSE or DTS. The majority of patients in the DiSE populations were males, and the prevalence of risk factors was somewhat lower than in the other two populations. Patients undergoing DTS more often had current stable angina pectoris, history of heart failure, diabetes, and a positive test result than patients undergoing DSE or DiSE testing (Table 1). There were also differences in the incidence of adverse cardiac outcome: 43 patients had events (3.9%) among 1093 patients undergoing DSE, 14 (3.6%) in 394 patients with DiSE and 81 (11.5%) in 717 patients undergoing DTS.

Predictive value of clinical risk factors

The relation between clinical variables and the incidence of the composite endpoint is shown in Table 2. Patients with current stable angina, a history of MI or diabetes had more than a 2-fold increased risk of perioperative cardiac events than those without such a history. A history of heart failure was another important clinical determinant of perioperative cardiac complications associated with a 4-fold increased risk in patients with such a history compared to those without. Surprisingly, advanced age was not

Table 1. Clinical characteristics of the patient populations.

Clinical characteristics*	DSE	DiSE	DTS	*p* value
Patients' no.	1093	394	717	
Demographics				
Age ≥ 70 years	557 (51%)	159 (40%)	301 (42%)	<0.001
Men	851 (78%)	356 (90%)	347 (48%)	<0.001
History §				
Current or stable angina pectoris	222 (20%)	51 (13%)	185 (26%)	<0.001
History of myocardial infarction	473 (43%)	86 (22%)	215 (30%)	<0.001
History of congestive heart failure	70 (6%)	–	34 (4.7%)	0.120
History of diabetes mellitus	168 (15%)	37 (9%)	149 (21%)	<0.001
Test result †				
Test positivity	216 (20%)	65 (17%)	198 (28%)	<0.001
Outcome				
Cardiac death or myocardial infarction	43 (3.9%)	14 (3.6%)	81 (11.5%)	0.001

* DSE, dobutamine stress echocardiography; DiSE, dipyridamole stress echocardiography; DTS, dipyridamole thallium perfusion scintigraphy; Ellipse indicates that data is not available.
† Test positivity of DSE and DiSE were considered positive if new wall-motion abnormalities occurred; and for DTS if images exhibiting defects, which partially or completely redistributed on delayed (>3 h) images.
§ For definition of clinical risk factors see "Methods" section.

Table 2. Univariable and multivariable relation between clinical baseline characteristics and perioperative cardiac death and myocardial infarction.

Clinical variables*	Event ($n=138$) § (%)	No event ($n=2053$) (%)	Univariable odds ratio (95% CI)	Multivariable odds ratio (95% CI)
Age ≥ 70 years	71 (51)	939 (46)	1.3 (0.9–1.8) †	1.3 (0.9–1.9) †
Current or stable angina pectoris	51 (37)	403 (20)	2.4 (1.7–3.4) ‖	2.0 (1.3–2.9) ‖
History of myocardial infarction	72 (52)	699 (34)	2.1 (1.5–3.0) ‖	1.6 (1.1–2.4) ‡
History of heart failure	17 (12)	87 (4)	4.5 (2.5–8.2) ‖	2.4 (1.4–4.3) ‡
History of diabetes mellitus	40 (29)	310 (15)	2.3 (1.6–3.4) ‖	2.1 (1.4–3.1) ‖

* Numbers may not add to 2204 due to missing data; For definitions of the clinical variables see "Methods" section; CI, confidence interval.
§ Event is specified as a composite of cardiac death and nonfatal myocardial infarction.
† $p > 0.05$; ‡ $p < 0.05$; ‖ $p < 0.001$.

Table 3. Univariable and multivariable models to predict perioperative cardiac death or myocardial infarction.*

Variables	No. of Patients	Event, No. (%)	Univariable Odds Ratios (95% CI)	Multivariable Odds Ratios (95% CI)	Multivariable χ^2	p value
Clinical risk score						
Score 0	539	16 (3.0)	1.0	1.0		
Score 1 to 2	1416	81 (5.7)	2.0 (1.1–3.4)	1.8 (1.0–3.0)	4.0	0.045
Score 3	236	41 (17.4)	6.9 (3.8–12.7)	4.6 (2.5–8.6)	23.7	<0.001
Stress echocardiography summary §						
No new wall-motion abnormalities	1206	16 (1.3)	1.0	1.0		
New wall-motion abnormalities	281	41 (14.6)	12.7 (7.0–23.0)	10.1 (5.5–18.5)	56.7	<0.001
Perfusion scintigraphy summary §						
No reversible perfusion defect	519	48 (9.2)	1.0	1.0		
Reversible perfusion defect	198	33 (16.7)	1.9 (1.2–3.2)	1.6 (0.9–2.6)	3.4	0.066

* Numbers may not add to 2204 due to missing data; Event, defined as a composite of cardiac death and nonfatal myocardial infarction; Variables that composed the clinical risk score were advanced age, current or stable angina, a history of myocardial infarction, a history of congestive heart failure and diabetes mellitus.
§ In the multivariable analysis dummy variables were introduced in order to account for the fact that patients with stress echocardiography did not undergo perfusion scintigraphy, and patients with perfusion scintigraphy did not undergo stress echocardiography.

significantly associated with adverse perioperative cardiac outcome. The multivariable model showed that current or stable angina, a history of MI, heart failure and diabetes mellitus remained important independent determinants of cardiac outcome (Table 2). The multivariable odds ratios for current or stable angina, a history of MI, and diabetes slightly decreased, whereas the odds ratio for heart failure almost halved compared to its univariable estimate. Based on these results, a simple risk score was developed to aggregate the available clinical information. To compose the clinical risk score one point was assigned to each of the following characteristics: age ≥ 70 years, current or stable angina, history of MI, history of heart failure and diabetes. Despite the fact that advanced age was not a significant risk factor in the present analysis it was included in the risk score because of its confirmed predictive value in previous studies.[8,9] In all, 539 (25%) had a risk score 0, 1416 (64%) had an index of 1 to 2, and 236 (11%) had a risk score of 3 or more points. The incidence of the composite endpoint in these patients was 3.0, 5.7 and 17.4% ($p < 0.001$). Regression analysis revealed a 2-fold increased risk for the composite endpoint associated with a risk score 1 to 2, and an almost 7-fold increased risk associated with a risk score 3 or more points (Table 3). Additional multivariate analyses demonstrated the prognostic value of clinical risk scores.

Predictive value of a positive test result

Patients who had NWMAs during DiSE had a 37-fold (OR = 37.0 [95% CI, 8.1–170.1]) increased risk of adverse cardiac events compared to those without NWMAs during DiSE. The presence of stress-induced ischaemia during DSE also was associated with the risk of perioperative cardiac complications (OR = 9.6 [95% CI, 4.9–18.4]). A comparison of univariate standardised beta coefficients (DiSE, $[\beta = 3.6 \pm 0.8]$ vs DSE, $[\beta = 2.3 \pm 0.3]$) showed that there was no statistically significant difference in the predictive value of a positive test result for DiSE and DSE ($p = 0.12$). Therefore, pharmacologic stress

echocardiography was considered as a single test modality irrespective of the pharmacologic agent (dobutamine vs dipyridamole) used for inducing myocardial ischaemia. A regression analysis of a test positivity then revealed that patients with NWMAs during pharmacologic stress echocardiography were at significantly higher risk for cardiac death or MI (OR = 12.7 [95% CI, 7.0–23.0]) than those without NWMAs. The predictive value of a positive test result during DTS (OR = 1.9 [95% CI, 1.2–3.2]) had significantly lower prognostic value compared to pharmacologic stress echocardiography (pharmacologic stress echocardiography, [$\beta = 2.5 \pm 0.3$] vs DTS [$\beta = 0.7 \pm 0.2$]; $p < 0.001$).

In a univariate analysis, important determinants of perioperative cardiac complications were a presence of 1 to 2 and 3 or more risk scores, and positive test results for pharmacologic stress echocardiography and a positive test result for DTS (Table 3). In a multivariate analysis the clinical risk scores were combined with the test results, and only the scores themselves, and the presence of NWMAs remained important determinants of perioperative cardiac outcome. A presence of a positive test result for DTS lost most of its predictive power with respect to the composite endpoint (Table 3).

The logistic regression model with the clinical risk score had satisfactory ability to discriminate between patients who did and did not have a perioperative cardiac complication (c-index 0.66). The multivariable model that combined clinical data with test result had considerably better discriminating power with a c-index of 0.80.

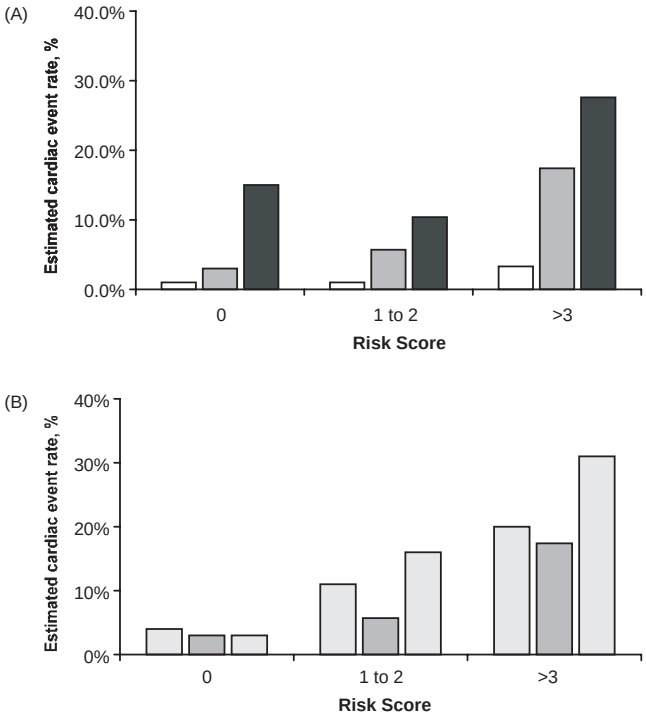

Fig. 1. Estimated risk of perioperative cardiac death or myocardial infarction based on clinical characteristics and results of pharmacologic stress echocardiography or dipyridamole perfusion scintigraphy. Panel A represents the estimated cardiac event rate (a composite of cardiac death and non-fatal myocardial infarction) based on the clinical risk score and the results of pharmacologic stress echocardiography. □ Negative pharmacologic stress echocardiography; ▒ Risk score; ■ Positive pharmacologic stress echocardiography. Panel B represents the estimated cardiac event rate (a composite of cardiac death and non-fatal myocardial infarction) based on the clinical risk score and the results of dipyridamole perfusion scintigraphy. □ Negative dipyridamole perfusion scintigraphy; ▒ Risk score □ Positive dipyridamole perfusion scintigraphy.

Risk classification model

Based on the results described above, a simple scheme was developed to estimate a patient's risk of perioperative cardiac complications (Fig. 1). If the clinical risk score was in the range of 0 or 1 to 2 points and stress echocardiography was negative, the estimated cardiac complication rate was low. The estimated risk of cardiac complications was also low in patients with risk score of 3 or more points without NWMAs (Fig. 1, panel A). Patients with a risk score of 0, 1 to 2 as well as 3 or more points, and with NWMAs were at a considerable risk (Fig. 1, panel A). In contrast, the magnitude of difference between negative and positive test results for DTS showed a different pattern. The prognostic value of DTS seemed to be dependent on the clinical risk profile of patients, but the formal statistical test of heterogeneity failed to show significance. This test had no predictive value in patients with a risk score 0, but its predictive value increased in patients with risk scores 1 to 2, and 3 or more points (Fig. 1, panel B).

Discussion

This study compared the additional prognostic capability of three noninvasive tests upon clinical risk factors used for perioperative cardiac risk assessment in large groups of patients who underwent major vascular surgery. The present analysis of 2204 major vascular surgery patients demonstrated that current or stable angina, a history of myocardial infarction, heart failure and diabetes mellitus are the most important clinical determinants of perioperative cardiac death or MI. Pharmacologic stress echocardiography results were highly predictive of adverse

cardiac outcome irrespective of the pharmacologic stressor used, which also confirms the results of other investigations.[6,7] In contrast, the prognostic value of DTS results was more likely to be dependent on patients' clinical risk profile.

Clinical risk factors for cardiac complications

Preoperative cardiac risk assessment of patients undergoing major vascular surgery is one of the most challenging and controversial areas of clinical medicine. Several large studies demonstrated that perioperative cardiac complications are particularly high in patients undergoing major vascular surgery.[2,6,7] Patients are at particularly high risk when they are $\geq$70 years old, and have a history or symptoms of CAD. In the present study, the selected group of risk factors stratified patients into low-, intermediate- and high-risk groups for cardiac complications. However, clinical variables alone did not provide an adequate power for stratification. Using pharmacologic stress echocardiography patients could be effectively stratified into group with very low estimated cardiac complication rate. The additional value of DTS imaging upon clinical risk factors showed a different pattern. Patient with a negative DTS results did remain at high risk for cardiac complications and there was no difference in the event rate between patients who had and did not have a perioperative adverse cardiac outcome.

Pharmacologic stress echocardiography

Pharmacologic stress echocardiography with dobutamine or dipyridamole is now widely accepted as an alternative stress test for patients unable to exercise. Stress echocardiography with dobutamine has proven to be a useful method for detection of CAD, and as a predictor of perioperative cardiac events in patients undergoing vascular surgery.[7–9] In contrast to other coronary vasodilators, dobutamine directly increases myocardial oxygen demand through positive chronotropic and inotropic effects, and also impairs myocardial oxygen supply by reducing the duration of systole. These factors may induce ischaemia if supply cannot meet the increased demand. The addition of atropine further increases heart rate and improves the sensitivity of the test without increasing side effects. In contrast to dobutamine, dipyridamole induces coronary hyperaemia, which leads to coronary steal[22] and can result in myocardial ischaemia characterised by stress-induced regional dysfunction. In theory, stress echocardiography with dipyridamole is considered less effective in inducing new wall motion abnormalities, especially for milder forms of CAD.

However, in our study there was not statistically significant difference in the predictive value of a positive test result for dipyridamole vs dobutamine stress echocardiography. The present study confirmed the findings of a small-scale study, which directly compared dipyridamole vs dobutamine stress echocardiography.[23] They found that the two tests had excellent negative predictive values for perioperative cardiac events and similar comparable positive predictive values.

Dipyridamole perfusion scintigraphy

The most extensively studied non-invasive approach to the cardiac risk stratification is DTS in combination of clinical risk factors. The presence of dipyridamole induced flow heterogeneity has been shown to be highly sensitive for the detection of coronary stenoses.[17] In practice, it implies that significant coronary stenoses are rarely missed, thus allowing a negative DTS imaging test to have a high predictive value for patients having no cardiac events after surgery.[2,19,20] In the present study, the prognostic value of DTS results was more likely to be dependent on patients' clinical risk profile. In patients at low-risk for cardiac complications test results did not differentiate between those who did and did not have a cardiac complication. In part, this observation suggests that the specificity of scintigraphy is less satisfactory compared to pharmacologic stress echocardiography. Artefacts and possible inclusion of unselected group of patients at high risk for false-positive perfusion scintigrams may have influenced the observed prognostic value of the test. Thus, it seems that DTS should be performed in patients at higher risk for cardiac complications such as patients with 1 to 2, or 3 or more cardiac risk factors.

Our study also revealed that a positive DTS result had significantly lower prognostic value than pharmacologic stress echocardiography. In agreement with our findings, current evidence suggests that the available data from direct comparison of dipyridamole echocardiography testing vs perfusion imaging suggest that perfusion defects are more frequent than transient dyssynergies and have a lower predictive value.[5] There are no studies to date that directly compare DSE and DTS in the same patient population. Hence, comparison of these two noninvasive tests can only be derived from the published reports. A recent meta-analysis comparing DSE and DTS concluded that the prognostic value of the two

noninvasive stress imaging was similar between DSE and DTS but accuracy varied with CAD prevalence.[24]

Study limitations

This study has certain limitations, which should be considered when interpreting the results. Three different noninvasive tests were compared for their ability to predict the incidence of perioperative cardiac events in three separate patient populations studied at different points in time in different hospitals. In order to study their relation to clinical risk factors, test characteristics the three datasets were combined. The differences in the prevalence of selected risk factors between the datasets, and the fact that patients were selected at different points in time in different hospitals may have biased the estimation of the predictive value of each test. However, by merging the datasets major vascular surgery patients in the present study could represent a wider range of patients.

In the present study DTS patients underwent planar perfusion scintigraphy, which reflects the available imaging technique at that time. Since then, single-photon computed tomography (SPECT) has been introduced.[25–27] Baron *et al*., however, questioned the predictive value of SPECT. They found that it did not provide additional prognostic information over clinical risk factors.[25] Thus, we assume that our results remain applicable.

Due to the retrospective nature of this study information on risk factors such as smoking, hypertension and renal failure were not available in all datasets as well as the use of concomitant cardiac medication in the two of the three datasets was unavailable. Including information on these risk factors and perioperative cardiac medication such as beta-blockers could help to further elucidate the nature of the predictive values of these three noninvasive tests.

Conclusion

This study confirmed the utility of clinical risk factors and additional non-invasive testing in preoperative management of patients undergoing major vascular surgery. The decision between myocardial perfusion imaging and stress echocardiography either with dobutamine or dipyridamole is influenced by numerous factors. Stress echocardiography has many practical advantages over nuclear perfusion imaging-due to its lower costs, wider availability, reduced imaging time, and absence of radiation exposure. The results of the present study suggest that pharmacological stress echocardiography either with dipyridamole or dobutamine appears to have more favourable prognostic performance, irrespective of clinical risk profile. In contrast, the prognostic value of DTS results was more likely to be dependent on patients' clinical risk profile. In order to confirm these findings future randomised clinical trials with large number of patients are necessary. The physician's choice of preoperative cardiac testing, however, should also take into account factors such as local expertise and experience, availability, and costs.

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